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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/211,691	12/14/1998	MICHEL GILBERT	14137-129-10	9572

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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 05/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/211,691	GILBERT ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER APPEAL BUT BEFORE A BOARD DECISION

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 3-13-06 has been entered.

Claims 37-51 are currently pending and are present for examination. Claims 49-51 have been filed as new claims.

Applicants' amendments and arguments and Declaration by Dr. Paulson, filed on 3-13-06, have all been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically , in view of the arguments presented by the applicants as well as the Declaration by Dr. Paulson, Examiner has withdrawn the rejection under 35 U.S.C. 103(a). However, based on those very same arguments and the Declaration by Dr. Paulson, Examiner has now reinstated new rejections under 35 U.S.C. 112, 1st paragraph.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 49-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 49-51 recite the phrase "amplified by a first primer of SEQ ID NO:3 and a second primer of SEQ ID NO:4" and "amplified by a first primer of SEQ ID NO:5 and a second primer of SEQ ID NO:6", "amplified by a third primer of SEQ ID NO:5 and a fourth primer of SEQ ID NO:6" respectively. The metes and bounds of the above phrase is not clear to the Examiner. It is not clear whether the primer used is a subsequence of either SEQ ID NO:3,4, 5, or 6 or whether the full length of said sequences is used as a primer. Furthermore, claim 51 recites a third and a fourth primer from the same SEQ ID NOs and for the same enzyme. It is not clear to the Examiner as to how the same primers can be used a third and a fourth primer and what is the difference between "first and second" and the "third and fourth" primers. Examiner requests clarification.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide that encodes a fusion polypeptide wherein the fusion polypeptide comprises a) a *Neisseria meningitides* α-2,3-sialyltransferase that catalyzes the transfer of a sialic acid, from CMP-Neu5Ac, to an acceptor molecule; and

b) a *Neisseria meningitides* CMP-Neu5Ac synthetase that catalyzes the formation of CMP-Neu5Ac from Neu5Ac and CTP, does not reasonably provide enablement for polynucleotide

encoding a fusion protein comprising any or all α-2,3-sialyltransferase and any or all CMP-Neu5Ac synthetase, isolated from any or all sources, including mutants, variants and recombinants of said enzymes made by using the primers SEQ ID NO:3-6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 37-51 are so broad as to encompass any polynucleotide encoding a fusion protein comprising any or all α-2,3-sialyltransferase and any or all CMP-Neu5Ac synthetase, isolated from any or all sources, including mutants, variants and recombinants of said enzymes made by using the primers SEQ ID NO:3-6. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of α-2,3-sialyltransferases and CMP-Neu5Ac synthetases broadly encompassed in the claimed encoded fusion protein. First of all, claims encompass mutants, variants and recombinants of any or all α-2,3-sialyltransferases and CMP-Neu5Ac synthetases. However, it is well known in the art that the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in

the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of the above enzymes isolated specifically from a single source i.e., *N.meningitides*. It would require undue experimentation of the skilled artisan to make and use the variant and mutant polypeptides and their respective polynucleotides to make the claimed fusion polynucleotide. The specification is limited to teaching the use of polynucleotides isolated from *N.meningitides* and encoding the above enzymes to make the fusion polynucleotide but provides no guidance with regard to the making of variants and mutants of the same or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim. While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In

addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

Next, applicants themselves have argued that not all fusion polypeptides encoded by fusion polynucleotides work in the same fashion. While some fusion polypeptides encoded by a fusion polynucleotide work as bi-functional proteins, some others fail to work as expected. Applicants have argued at length traversing the previous obviousness rejection which the Examiner maintained based on the teachings of Bulow et al. and the proximity effect reported in that reference. Dr. Paulson in his Declaration has clearly explained that when the instant application was filed in 1997, questions had been raised about the validity of proximity effect disclosed in Bulow et al. which relies on diffusion or Brownian motion for transport of a reaction intermediate between two active sites on a bi-functional fusion protein. Dr. Paulson explains that researchers demonstrated that Brownian motion was not sufficient to transfer a coupled reaction intermediate from the active site of one protein to the active site of its fusion partner and that researchers then proposed that the arrangement of charged residues on a fusion protein allowed electrostatic surface diffusion or channeled transfer of an intermediate from the active site of one protein to the active site of its fusion partner and that this channeled transfer or substrate channeling was believed to enhance reaction kinetics and explain the so-called proximity effect. The Declaration also explains that researchers were not able to reproduce even that kind of substrate channeling in a synthetic bi-functional fusion protein, even though the structure of a naturally occurring bi-functional fusion protein, the *Leishmania* dihydrofolate reductase-thymidylate synthase (DHFR-TS) expressed in *E. coli* as two separate mono-functional enzymes was available as a model. The Declaration explains that the synthetic

E. coli DHFR-TS bi-functional fusion protein did not exhibit substrate channeling and that Trujillo et al. concluded that "the local concentration of H_2-folate obtained by linking the mono-functional *E. coli* enzymes is not sufficient to promote substrate channeling" thereby demonstrating that substrate channeling, i.e., a proximity effect, did not occur in the synthetic *E. coli* DHFR-TS fusion protein. The Declaration also concludes that that any "advantage" resulting from alleged proximity effects is not conserved during evolution i.e., it cannot be expected of any or all fusion proteins. The Declaration further goes on to state that the proximity effect could not reliably be generated in synthetic fusion proteins, and the proposed advantage of a bi-functional fusion protein over mono-functional proteins was doubted and that papers that build on the results of Trujillo et al. and discredit the proximity effect continue to be published. The Declaration finally states that a co-author of Bulow et al. paper has now concluded that "bringing two sequential enzymes together in a fusion protein . . . is obviously not sufficient to cause any kinetically significant metabolite channeling through proximity effects."

Therefore based on the Declaration of Dr. Paulson et al. Examiner takes the position that not any or all enzymes can be simply made as a functional fusion protein with bi-functional activities and that is possible to do so only with specific polynucleotides encoding specific polypeptides.

The specification does not support the broad scope of the claims which encompass polynucleotides encoding a fusion protein comprising any or all α-2,3-sialyltransferases and CMP-Neu5Ac synthetases including variants and mutants of enzymes obtained by using the primers SEQ ID NO:3-6 because the specification does not establish: (A) regions of the two proteins in the fused structure which may be modified without affecting the bi-functional

activity; (B) the general tolerance of α-2,3-sialyltransferases and CMP-Neu5Ac synthetases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue on any or all of α-2,3-sialyltransferases and CMP-Neu5Ac synthetases with an expectation of obtaining the desired biological function (bi-functional); and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including α-2,3-sialyltransferases and CMP-Neu5Ac synthetases with an enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of α-2,3-sialyltransferases and CMP-Neu5Ac synthetases having the desired biological characteristics for making it as a fusion protein is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 37-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 37-51 are directed to polynucleotides encoding fusion polypeptides wherein said fusion polypeptide comprise α-2,3-sialyltransferases and CMP-Neu5Ac synthetases. Claims 37-51 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polynucleotides derived any or all sources including any or all *Neisseria* including modified sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue/nucleotide that have not been disclosed in the specification. No description has been provided of the polynucleotide sequences encoding modified polypeptide sequences as encompassed by the claim. No information, beyond the characterization of a fusion polynucleotide encoding *Neisseria meningitides* has been provided by applicants which would indicate that they had possession of the claimed genus of polynucleotides. The specification does not contain any disclosure of the structure of all the polynucleotide sequences derived from, *Neisseria meningitides* including fragments and variants within the scope of the claimed genus. The genus of polynucleotides claimed is a large variable genus including sequences which can have a wide variety of structure. Therefore many structurally unrelated polynucleotides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

May 17, 2006